REMARKS

Claims 61-63, 65, 67-70, 75, and 77 have been amended. Claim 60 has been withdrawn from consideration. Claims 61-79 are presented for examination and will be pending in the application upon entry of the amendments presented herein. Claim 60 will remain pending but withdrawn from consideration.

Objections to the Claims

Claims 61-62 and 70 are objected to because of inconsistent use of "wild-type" and "wild type." Applicants have deleted this term from those claims.

Claim 65 has been corrected to insert an article between "lacks" and "UL9 gene."

Claim 69 has been amended to more clearly indicate that it is "the rHSV of claim 61 which is a recombinant derivative of HSV-1 strain 1802" in accordance with the Examiner's suggestion.

Rejection under 35 USC §112, Second Paragraph

Claims 61-62, 69, 71 and 75 are rejected under 35 U.S.C. §112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

The term "wild-type" or "wild type" has been deleted from Claims 61-62 and 70. In claim 61, the descriptor "corresponding HV sequence lacking the *rep* and *cap* sequences" has been added in accordance with the Examiner's suggestion.

Claim 69 has been amended to change the dependence to claim 67 in order to provide proper antecedent basis.

Claim 75 has been amended to correct improper antecedent basis.

Rejections under 35 USC §112, First Paragraph

Amended claim 61 is rejected as unsupported for using the term "expression vector" Applicant has amended claim 61 (63, 69-70 and 73 as well) to use the term "expression cassette" as suggested by the Examiner.

Claim 61 is amended to specify the minimum number of consecutive dilution steps in the plaque assay as recited in the specification where no reversion to wild type was observed.

Claim 62 is amended to recite "up to 20%" of the titer of wild type herpes for which the Examiner notes there is literal support in the specification.

Claim 69 is rejected under 35 USC §112, first paragraph, as failing to comply with the enablement requirement. The Action's position is that HSV-1 strain 1802 is not sufficiently described in the specification to allow its use.

According to the Examiner, the biological material "..must be obtainable by a reproducible method set forth in the specification or otherwise known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809." (page 7 of the Office Action). The Examiner further notes that that if biological material is not available, the requirements of 35 U.S.C. 112 may be satisfied by a deposit of the biological material that meets the requirements of 37 CFR 1.801-1.809.

Both requirements have been fulfilled by Applicant. A biological deposit of rHV 1802 was made before the filing of the application on November 10, 1997, which is before the July 6, 1998 filing date of the application. The deposit was made in an International Depositary Authority (IDA) established under the Budapest Treaty, which is recognized as acceptable for the purposes of fulfilling the requirements under 37 CFR 1803. Under MPEP 2405, under "Current IDAs", the following is listed IDA has been recognized under the Budapest Treaty:

European Collection of Cell cultures (ECACC)
Vaccine Research and Production Laboratory
Public Health Laboratory Service
Porton Down
Salisbury, Wiltshire, SP4 0JG
United Kingdom

Applicant directs attention to page 24 in the instant application where deposit information is found at lines 8-11:

European Collection of Cell Cultures
CAMR
Salisbury
Wiltshire SP4 0JG
UK

Applicant at lines 9-11 additionally sets forth the date of deposit as November 10, 1997 and an assigned provisional access number V97111302.

Because the Action has based a rejection based on a purported lack of availability, Applicant's representative hereby averrs that that the deposited material was accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon granting of the patent.

Applicant will amend the specification to provide the complete taxonomic description of the biological material and the permanent accession number when this information is received from the ECACC (from which request has been lodged).

Applicant submits that HSV-1 is fully described in the specification to the extent that Applicant has referenced publications readily obtainable by the public and from which one of ordinary skill in the art could readily construct the 1802 mutant HSV.

The nucleic acid sequence for strain HSV 1802 was available to the public at the time the application was filed. McGeoch, *et al.*, 1986 (Reference CF on form 1449) describes the HSV-1 DNA as a "linear double stranded molecule of some 155,000 base pairs, regarded as comprising two covalently joined segments, termed the long regions (cite omitted)."

Figure 2 in the McGeoch, *et al.* publication shows the 6633 base pair sequence for the short region. This is the region into which a unique restriction enzyme site, *Xba*I, was engineered.

With the sequence of the short region in hand, the person of ordinary skill could refer to Rixon and McLauchian (reference CE on Form 1449), and proceed to prepare the 1802 mutant described in the present application. On page 2933, Rixon and McLauchian describe how a unique *Xba*I site was engineered into HSV-1 from which the four naturally occurring *Xba*I sites had been removed (citing Maclean & Brown, 1987, fully referenced in the paper). Rixon and McLauchian refer to the HSV-1 strain lacking these four restriction sites as "1702". Once in hand, the 1702 was engineered as described to restore the TK+ phenotype and to insert a unique XbaI site (see Figure 1) where the *Xba*I replaces *Rsa*I, characterizing the 1802 mutant.

Applicant believes that the information on sequences, how and where to insert the unique retriction site and the level of skill and knowledge at the time of filing the application are more than adequate to allow the skilled artisan to make and use mutant HSV-1 1802.

As stated in the response of 12/30/04, Applicant submits that HSV-1 strain 1802 is fully described in the specification, taking the cited references into consideration for specific details and showing that the 1802 construction was known. On page 7, line 25, reference is made to 1802 as having a unique X*bal* restriction site in the Us region at position 143 969, also pointing out that the positions are numbered in accordance with the McGeoch, *et al.* reference (page 7, line 28). Using this mutant, a construct containing the *rep* and *cap* genes in accordance with the invention is shown in FIG. 1. Page 12, line 35 states that the AAV

genome is numbered in conformity with Genbank deposit number J01901. Thus the 1802 mutant can be readily made and used by those skilled in the art to insert AAV *rep* and *cap* genes into the HSV genome because there is ample description and guidance in the specification, including the references, to do so.

Accordingly, Applicant believes the application is in full compliance with the requirements set forth in 37 CFR §§1.801-1.809, either by fulfillment of the Biological Deposit requirement, or by information known and available to the public at the time of filing of the application..

Copies of the McGeoch, *et al.* and Rixon and McLauchian references have previously been made available to the Examiner.

Rejection under 35 USC §102

Claims 32-39 and 41-60 are rejected under 35 USC §102(b) as anticipated by the Dong, *et al.* reference (WO 95/06743) for reasons of record and summarized in the Action from selected references to the text of the Dong, *et al.* published international application. Applicant respectfully disagrees that Dong is anticipatory.

The Action's position is that the Dong reference teaches 1) construction of helper viruses from any herpesvirus; (2) the helper viruses can be either replication competent or replication defective; (3) herpes helper viruses can include one or more of *rep, lip* and *cap* genes; (4) essential or non-essential genes from the helper virus genome have been deleted; (5) helper viruses can promote expression of essential AAV genes with wild type or heterologous promoters; (6) the particular herpes virus is not crucial; (7) *rep, lip* and *cap* could be included into a herpes virus genome; (8) the R7020 mutant has a deletion of approximately 700 bp from *tk* gene and all bp from end of IE63 gene to a4 gene; (9) the *rep, lip, cap* sequences can be inserted into at least either of two positions that include site between the inserted tk gene and HSV-2 DNA sequences and the site of the *tk* gene deletion.

A rejection based on anticipation or lack of novelty requires that the same invention, including each element and limitation of the claims, was known and used by others prior to the instant invention; *i.e.*, the anticipating reference "must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996). Applicant maintains that Dong does not disclose every element of the challenged claims.

Applicant continues to hold the position that Dong does no more than teach broad concepts for designing and constructing recombinant herpesviruses containing *rep* and *cap* genes. Certainly Dong describes textbook procedures in the form of a general literature review; *e.g.*, in Example IV (never actually done) where generation of replication-competent recombinant adenovirus carrying *rep*, *lip* or *cap* separately is described. In summarizing the "example" Dong states:

> Recombinant adenoviruses carrying the *rep-lip* or *cap* gene are generated by *in vivo* homologous recombination of pFG*rep* or pFG*cap* with purified adenovirus DNA which has been digested with *Eco*R1 restriction enzyme. The detailed procedure is essentially the same as that described by ...

Not only is the example prophetic, but as was well-known at the time the application was filed, homologous recombination is not predictable; and in fact is the reason why wild type virus is obtained when only the recombinant virus is desired. Additionally, Dong's "teaching" is that one makes recombinant adenovirus (not AAV) with either the *cap* or the *rep-lip*.

The Dong reference is replete with general instructions, mainly directed to adenovirus, with a single exemplary reference to recombinant herpes family viruses (Example VI). In this example, Dong provides no evidence that *rep*, *cap* HSV constructs such as those of the present invention can be engineered and will replicate. Again, referring to the literature, Dong chooses a known mutant (described by Mocarski, *et al.* (1980) and Post and Roizman

(1981) and makes the unsubstantiated statement that "...the *rep-lip-cap* genes of AAV can be inserted in, at least, either of the two positions." There is no evidence that this was done. It is wishful thinking. A general recitation of "how to" procedures, none of which were carried out by Dong, is insufficient to defeat novelty of the present invention.

One of the important features of applicant's recombinant herpes virus is that there is no reversion to wild type under replication conditions. Dong makes no mention of any such feature or expectation in any of the proposed multitude of constructs one might contemplate in attempting to engineer and produce the presently claimed recombinant herpesviruses. It cannot be argued that this feature is inherently present in the HSV constructs that someone might make by picking and choosing from the range of possibilities recited in Dong, many of which do not even apply to HSV (see Example VII where Adenovirus is employed).

Dong never made or even explicitly taught how to make the recombinant herpes virus of the present invention. There is no evidence in Dong that any construct, even those described in detail, would not revert to wild type or even that Dong contemplated that reversion to "wild type" should be considered in engineering recombinant herpesviruses.

Anticipation requires that Dong expressly disclose the lack of reversion to wild type by describing constructs in sufficient detail to enable the claimed invention, including all claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. See *Crown Operations International, Ltd. v. Solutia Inc.* 289 E2d 705, 708, 15 USPQ2d 1917, 1921 (Fed. Cir. 2002).

In responding to a dissent, the Court in *Elan Pharmaceuticals, Inc. and Athena Neurosciences, Inc. v. Mayo Foundation for Medical Education and Research* (August 30, 2002), reiterated its basic premise that "...a novel product is not 'anticipated' if it did not previously exist." It matters not that one could pick and choose among all the possibilities in Dong. Anticipation is not fulfilled by a general proposal to make a product that has not

been made or which is not so described that, when made according to explicit steps or directions, the characteristics are inherent to the structure. Dong does not anticipate applicant's claimed invention. Applicant's subject matter was not previously known because Dong did not describe each and every element of the claimed recombinant herpes virus nor has Dong provided enablement for others to make Applicant's invention.

Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Rejection under 35 USC §103

Claim 65 is rejected under 35 U.S.C. §103(a) as unpatentable over Dong *et al.* in view of Dargan, *et al.* (U.S. Pat. No. 5,994,116). The Action admits that Dong does not explicitly list the UL9 gene as being deleted in a replication-defective recombinant herpes virus, but relies on the naming of several HSV-1 essential genes, including UL9, in the '116 patent. The Action further takes notice that a cell line, A26, which expresses UL6-10, supports growth of UL8 or UL-9 deficient strains, concluding that not only would the skilled artisan have modified the information found in Dong to delete UL-9, but also would expect a replication-defective rHSV/AAV virus that does not replicate but provides *rep*, *lip* and/or *cap* gene products for packaging rAAV virions. The basis of the Action's conclusion is that there is no evidence that a construct such as Applicant's would not work.

Applicant respectfully disagrees and particularly strongly disagrees with the hindsight nature of the Action's conclusions. There is no evidence to suggest that by combining Dong and the '116 patent one would be motivated to delete UL-9, selecting a herpes virus, and somewhere inserting a *cap*, a *lip* and/or a rep gene into a non-essential region of the herpes genome would result in a replication deficient herpes that could provide *rep*, *cap*, *lip* gene products to an infected cell without detectable homologous recombination to the corresponding mutant virus (*i.e.*, lacking UL9).

To sustain a rejection based on obviousness, combination of prior art references in rejection of claimed subject matter requires consideration of two factors: (1) whether or not the prior

art suggests to one of ordinary skill in the art how to carry out the process and (2) whether or not the prior art would also have provided a reasonable expectation of success if the process was carried out as indicated or suggested, *In re Dow Chemical Co.*, 837 F.2d 469, 473 5 USPQ2d, 1529, 1531 (Fed. Cir. 1988).

It is Applicant's position that neither Dong nor the '116 patent disclose explicitly or implicitly how to carry out the claimed invention. No detailed enabling methodology is stated for the practice of the invention, in contrast with such cases as *In re O'Farrell*, 853 F.2d 901-902, 7 USPQ, 1679 1680 where an explicit suggestion of how to and what to substitute to practice the claimed invention was set forth. In the present case, neither reference explicitly suggests *rep* and *cap* genes each operatively linked to a promoter within an expression cassette integrated into a non-essential region of the herpes virus genome. Dong merely provides general information, such as "...choice of promoter is not believed to be particularly critical..."; "...replication-defective ...herpes virus vectors which include the AAV *rep*, *lip* and *cap* genes, along with the AAV P5 promoter..." (p. 9); "...will generally be adenoviral or herpes (HSV, PRV and CMV)...however, any DNA segment or gene may be employed as a transgene..."

Dong does not even suggest Applicant's recombinant HSV in Example VI. Dong describes a vector created by others (R7020) broadly stating, for example, that this vector "...lacks approximately 700 bp form the domain of the thymidine kinase (tk) gene and all of the sequences from..." (emphasis added) page 44. This is hardly enabling, even when Dong continues by generally stating that "In R7020, or a similar recombinant, the *rep-lip-cap* genes of AAV can be inserted in, at least, either of the two positions." Dong goes on to say that the sites are between the inserted tk gene (which apparently is in place of the ITRs) and the HSV-2 DNA sequences, and then opines how genes of interest can be included at positions different from that of the essential AAV genes. It is clear that this "described" recombinant HSV, is different from Applicant's, has not been made and that Dong makes no specific suggestion to make Applicant's construct. The only information gained from the '116 patent is that the herpes virus will not replicate when an essential gene is mutated,

(emphasis added) in this case UL8. A temperature sensitive mutant, UL9, apparently was able to replicate in a cell that provided UL6-10 genes. The interesting aspect of the '116 publication is that the work to identify "essential genes" involved mutants, not deleted genes. This alone provides no basis to combine Dong and '116 because the '116 patent simply disables a gene (in one case by what appears to be a point mutation) and provides no motivation to delete a gene.

The combination of Dong and the '116 patent, if anything, teaches away from the invention in claim 65. In accordance with '116, one should mutate UL8 or UL9, but there is no suggestion that one should delete the UL9 gene in order to obtain a replication-defective virus.

The second prong of the obviousness test is motivation to combine the references. There is simply no motivation to combine the '116 patent with Dong. The '116 patent is even broader in concept than Dong because the UL8 replication defective HV particles are defective because the single serine codon at 267 is replaced with an amber stop codon. The person of ordinary skill would simply recognize that this might be a way to make a replication defective HV; but that person not be motivated to delete UL9 or to combine this with the broad teachings in Dong to make a recombinant adenovirus or herpes virus.

Therefore there is no basis to cite the '116 patent to teach replication-defective HV lacking the UL9 gene. Accordingly Applicant respectfully requests reconsideration and withdrawal of the rejection.

Amendments to the Claims

Claims 61, 62-63, 65 and 75 have been amended in substantial part in accordance with the Examiner's suggestions. It is believed that the other amendments are not substantive and are for better claim form (*e.g.*, claim 67). Claim 69 has been amended to include Deposit accession information to clearly distinguish the recombinant herpes virus. Claim 70 has been amended to incorporate the description of the plaque assay suggested by the examiner

and to relate more closely to claim 61, which is directed to the recombinant HV. No new matter has been added.

Conclusion

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of all pending rejections with allowance of claims 61-79. If upon consideration of the foregoing arguments, the Examiner is not inclined to allow the application, Applicant respectfully requests a personal interview with the Examiner and Applicant's attorney and invites the Examiner to call the undersigned as the telephone number indicated below.

6-20-2005

Respectfully submitted,

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